Effect of natural honey on lowering lipid profile

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ABSTRACT

الأهداف: تمثل أمراض القلب والشرايين 31% من أسباب الوفاة بالعالم، وهناك براهين تتزايد بأن العسل قد يساعد على خفض الدهون في الدم والذي قد يساعد في عملية الوقاية من أمراض القلب والشرايين.

المنهجية: تم البحث في مايو 2020 لكل الدراسات المنضبطة المعشَّاة في المصادر الطبية الموثوقة. تم إدراج جميع الدراسات التي قامت بدراسة تأثير العسل على مستوى الدهون لأي فئة عمرية وبأي جرعة وطريقة. قام باحثان بمسح لنتائج البحث ومن ثم تقييمها حسب معايير إدخالها في المراجعة المنهجية، قام باحث ثالث بإبساء رأيه في حال كان قرار الباحثين مخلفين تجاه أية دراسة. هدف: تقييم البراهين المنشورة تجاه تأثير العسل الطبيعي بخفض مستوى الدهون في الجسم.

النتائج: تم استخراج 7 دراسات بواقع 370 مشارك تم قبولهم، ومن التحليل الجامع أظهر العسل أن له تأثير معتبر بإنقاص إجمالي الكولسترول بواقع 14.97 ملجم/ديسيلتر، أظهر التحليل اختلافا كبيرا بين الدراسات، كما كان للعسل أثرا في زيادة الدهون مرتفعة الكثافة بواقع 1.78 ملجم/ديسيلتر.

الخلاصة: أخذ العسل الطبيعي يقلل من الكولسترول العام، الدهون قليلة الكثافة، الدهون الثلاثية بشكل كبير، كما يزيد من الدهون عالية الكثافة. من الممكن أن يُقترح استخدام العسل للمرضى ذو ارتفاع مستوى دهون الدم، أما عن تأثيره في خفض الوفيات بسبب أمراض القلب والشرايين فذلك يستدعي عمل دراسات أكبر.

Objectives: To evaluate the available evidence of natural honey and its effect on improving lipid profiles among the adult population.

Methods: The following databases were searched in May 2020 for randomized controlled trials (RCTs) and crossover studies without any restrictions in language, publication year, or status: CENTRAL, Embase Elsevier, ClinicalTrials.gov, MEDLINE, the WHO International Clinical Trials Registry Platform, and Google Scholar. We included all RCTs and crossover studies that studied the effect of natural honey on improving lipid levels in individuals at any age, for any dose and duration. Trials investigated the intake of honey alone or honey dissolved in water. The comparison groups were no intervention or placebo. Two independent reviewers screened and evaluated the included trials. The third reviewer was involved in resolving any disagreement. Our aim was to evaluate the evidence available regarding the effect of natural honey in improving lipid profile.

Results: Seven trials with 370 participants fitted the inclusion criteria. Pooled analysis showed, honey was found to reduce total cholesterol levels with statistical significance (mean difference [MD]: -14.97 mg/dl, 95% CI: 19.61 to -10.32). Honey was associated with a statistically significant increase in high-density lipoprotein (HDL) levels (MD: 1.78 mg/dl, 95% CI: 0.68 to 2.88). There was a statistically significant LDL reduction level (MD: 18.99 mg/dl, 95% CI: -22.79 to -15.20). Finally, honey was found to lower triglyceride levels significantly (MD: 9.68 mg/dl, 95% CI: -15.56 to -3.80).

Conclusions: Total cholesterol was significantly reduced with the use of natural honey intake, as well as low-density lipoprotein (LDL), and triglycerides. High-density lipoprotein showed significant increment. Small quantity of honey can be recommended for patients with dyslipidemia. The impact on clinical outcomes such as cardiovascular mortality and morbidity needs to be evaluated in large studies.
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Keywords: honey, systematic review, meta-analysis, dyslipidemia, lipid, CVD.

The rate of CVD mortality represents 31% of total global deaths.[1] A healthy endothelium has vasodilatory, anti-inflammatory, and anti-atherogenic effects. When the endothelium function is impaired, platelet activation, thrombogenesis, cytokine adhesion, and inflammation will be dysregulated. This results in

atherosclerosis formation by plaques. Dyslipidemia, diabetes, and hypertension are well-known contributors to the pathophysiology and promote further damage to the endothelium.[2,3] Complete blockage or restricted flow caused by narrowed arteries, for which atherosclerosis is responsible, limits the amount of oxygen delivered to tissue and organs. In addition to the natural aging process, other factors such as high cholesterol, smoking, hypertension, torpid lifestyle and obesity may accelerate the hardening and narrowing of the arteries.[4]

Honey contains a heterogeneous class of chemical compounds that are defined as polyphenols.[5] These are further divided into 4 subcategories. Two of them in which honey is rich in non-flavonoids (phenolic acids) and flavonoids.[6] These substances are carrying antioxidant activities. They scavenge free radical. They form less toxic and stable molecules.[5] Nevertheless, various in and ex-vivo studies evinced anticancer, antifungal, antimicrobial, antidiabetic, and antiviral activity of honey. Its safeguarding actions on gastrointestinal, cardiovascular, respiratory, and nervous systems has also been evident.[7,8] Multiple mechanisms can accomplish the amelioration of CVD, for example, improving coronary vasodilatation, improving endothelial function, inhibiting platelet aggregation, reducing lipoprotein (LDL) oxidation, reducing inflammatory response, decreasing oxidative stress, and providing antioxidant protection.[9-15]

Evidence from observational and interventional studies is inconclusive regarding the effect of honey consumption on clinical cardiovascular risk factors such as lipid profile. In this systematic review and meta-analysis we aim to evaluate the available evidence of natural honey and its effect on improving lipid profiles among the adult population.

Methods. The following databases were searched in May 2020 for the word 'honey' for randomized controlled trials (RCTs) and crossover studies without any restrictions to language, publication year, or status: the Cochrane Central Register of Controlled Trials (CENTRAL), Embase, and MEDLINE. We also screened all reference lists. We have contacted the authors when we needed extra information.

We included all RCTs and crossover studies that studied the effect of natural honey on lipid profile in

participants without or with chronic illnesses at any age, for any dose and duration, in an outpatient setting. The trials investigated the intake of natural honey alone or honey dissolved in water. The comparison groups were no intervention or placebo. The outcome of interest was change in lipid profile, including total cholesterol, LDL, HDL, and triglycerides. To avoid confounding, we excluded trials involving multifactorial lifestyle interventions or honey mixed with anything in the control group.

We imposed no restrictions on type, dose, or formulation. We included the controls who received either placebo or no intervention. We included studies of any duration ranging from 4 weeks to 12 weeks.

Two reviewers independently evaluated the risk of bias (RoB) of all studies employing the Cochrane Collaboration's tool for assessing RoB. The reviewers screened the abstracts for inclusion criteria. Included articles were fully evaluated for the final inclusion decision. The third reviewer was involved in resolving any disagreement. The outcome measurements were descriptive measures reported as the difference in mean pre- and post-honey treatment and SD.

The RevMan 5.3 statistical package was utilized to pool the results of all included studies.

I^2 test was used to assess the heterogeneity and considered substantial when it was ≥50%. We estimated the weight of treatment effect by using random effect model to ensure the robustness of the results whenever there was substantial heterogeneity amongst studies. Potential sources of heterogeneity of treatment effect were explored. The confidence interval was set at 95% and a 2-tailed *p*-value of ≥0.05.

Results. Our search generated 1569 hits, and 497 were removed as duplicates. The titles and abstracts of 1072 were screened, 1056 were excluded, and 16 papers were identified for final exclusion or inclusion. Of them, we included 7 RCTs which met the criteria for inclusion. A diagram of the study flow details is given in **Figure 1**. **Table 1** elucidates the reason of excluded studies. The reasons for the exclusions were mainly short-term trial (less than 4 weeks), no control group, using honey in all trial arms, or an intervention that was not pure honey.

Table 2 presented the characteristics of all included studies and information about the duration, intervention, and the number of participants in each included study. The RoB is summarized in **Figures 2 & 3**.

Three hundred and seventy participants out of 7 trials with were included. Total number of the experimental group was 197 participants, and 173

Figure 1 - Characteristics of excluded studies.

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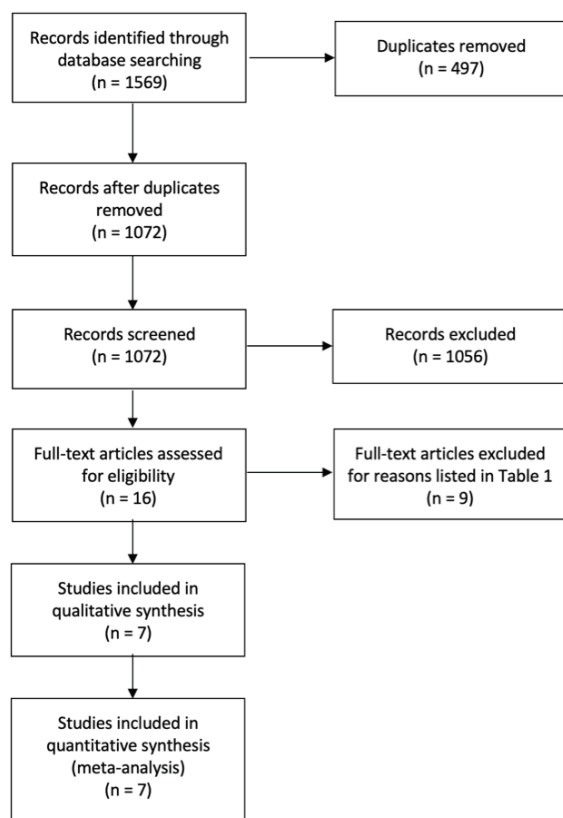
Study	Year	Reason for exclusion
Alemam et al[23]	2019	No control group
Al-Waili[24]	2004	No control group
Arani et al[25]	2018	Inappropriate comparator intervention (honey in both arms)
Bekkaye et al[26]	2016	No control group
Bhatti et al[27]	2016	No control group
Derakhshandeh-Rishehri et al[28]	2014	No pure honey
Despland et al[29]	2017	Short-term trial (the follow-up period was eight days)
Erejuwa et al[30]	2019	Still on-going study
Whitfield et al[31]	2016	Inappropriate comparator intervention (honey in all arms)

participants were in the control group. Approximately 20% of the participants were females. The duration of the studies ranged between 4 and 12 weeks. One study by Abdulrahman et al[16] included 20 pediatric participants with an age range of 4-18 years. One study was a randomized crossover clinical trial. The mortality and clinical events were not measured, as they were not included in the studies' objectives.

From the pooled analysis, statistically speaking, honey has significantly reduced total cholesterol levels (mean difference [MD] -14.97 mg/dl; 95% confidence interval [CI] -19.61 to -10.32); test for heterogeneity: $I^2 = 44\%$ (**Figure 4**). Intriguingly, honey has a statistical significance in raising the HDL levels when compared to control (MD 1.78 mg/dl; 95% CI 0.68 to 2.88); test for heterogeneity: $I^2 = 84\%$ (**Figure 5**). For LDL levels, the heterogeneity significantly existed between studies ($I^2 = 88\%$), and there was a statistically significant decrease in the LDL levels (MD -18.99 mg/dl; 95% CI -22.79 to -15.20) (**Figure 6**). Finally, honey lowered the level of triglyceride significantly (MD -9.68 mg/ dl; 95% CI -15.56 to -3.80); test for heterogeneity: $I^2 = 88\%$ (**Figure 7**).

Discussion. Our review, interestingly, revealed that the consumption of natural honey produced a statistically significant decrement in triglycerides, LDL, and total cholesterol. The review also showed that honey increased HDL significantly.

This review included adult participants and one study of the pediatric age group. All participants did not have the same baseline lipid profile. Both genders were included, with a majority of men over women. The effect of duration or "dose" of the intervention was not included in our results. Furthermore, because of the variation among the included studies of natural honey dosage consumed, we could not draw a conclusion about how many grams would be required to improve the lipid profile.

Some RoB was detected in the studies included in our review, it was mainly blinding bias, and therefore, cautious treatment of the results is mandatory. In half of the included trials, the methods of randomization were assessed to have low risk, whereas in all 7 trials the allocation concealment details were not declared. All studies demonstrated low RoB related to incomplete outcome. Selective outcome reporting bias was low in all studies. Judging the risk of other biases was not possible due to information insufficiency for all studies.

Due to the variation in doses, durations and forms of intervention in the included trials, small study bias is a risk in our review. Because of limited included trials, the publication bias was not tested in funnel plots. None

Table 2 - Characteristics of Included Studies.

| Study	Year	Duration	Participants	Interventions
Abdulrhman et al[16]	2013	Two 12 weeks (crossover)	20 pediatric patients of both sexes (F:M=1:1), aged 4–18 years, with insulin-dependent diabetes.	0.5 mL of honey per kg body weight daily compared with control group, who did not receive anything.
Bahrami et al[32]	2009	8 weeks	48 patients (13 men and 35 women), with type II diabetes.	Natural honey with doses indetails (1st 2 weeks, 1 g/kg/day; 2nd 2 weeks, 1.5 g/kg/day; 3rd 2 weeks, 2 g/kg/day; and the last 2 weeks, 2.5 g/kg/day) compared with no treatment for the control group.
Majid et al[33]	2013	4 weeks	70 healthy young males. 7 participants dropped out because of lifestyle changes during the study.	70 g of honey taken daily for 4 weeks period; control group was kept on the same diet as that of experimental group except honey.
Münstedt et al[34]	2019	4 weeks	60 male patients with hyperlipidemia.	75 g of honey compared with 75 g glucose and fructose solution with an identical content (honey-comparable sugar solution).
Rasad et al[35]	2018	6 weeks	60 healthy males, aged 18-30 years, non-athletic and non-smoker.	70 g natural honey solved in 250 mL tap water compared with 70 g of sucrose solved in 250 mL tap water daily.
Wan Ghazali et al[36]	2015	12 weeks	64 male smokers, aged 20-50 years.	20 g/day of Tualang honey compared with control group, who did not receive anything.
Yaghoobi et al[17]	2008	30 days	55 overweight or obese subjects, aged 20-60 years, 24 males and 31 females.	70 g of honey liquefied in 250 ml tap water compared with 70 g of sucrose dissolved in the same amount of water daily.
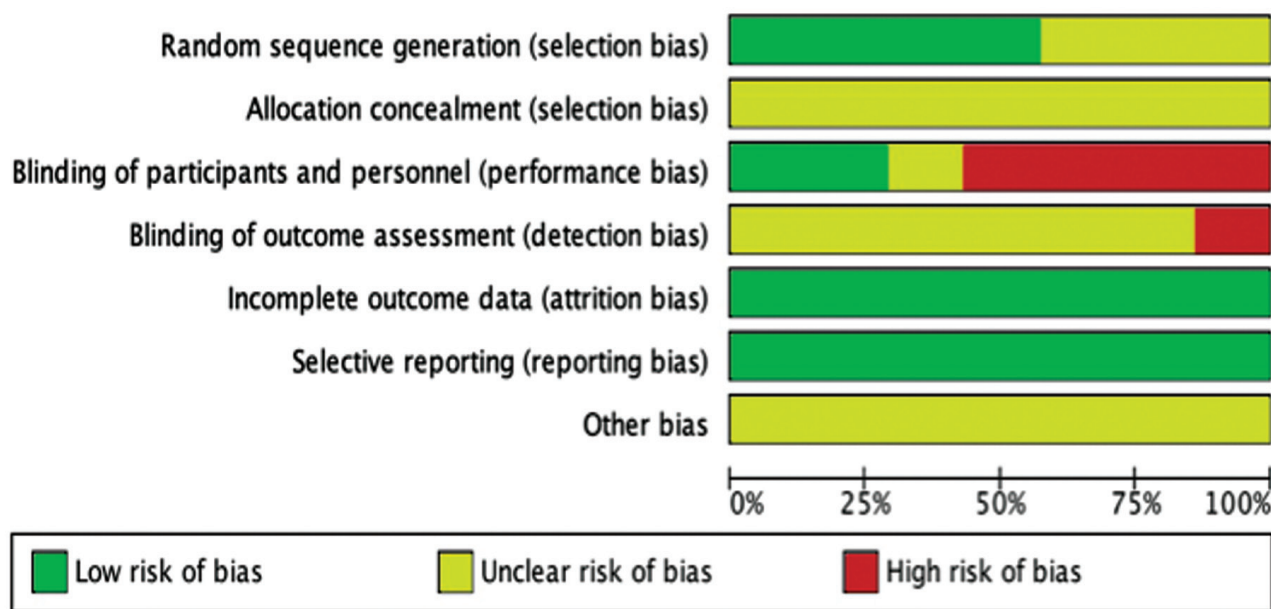
Figure 2 - Risk of bias graph showing the review of authors' judgements regarding each risk-of-bias item presented as percentages across all included studies.
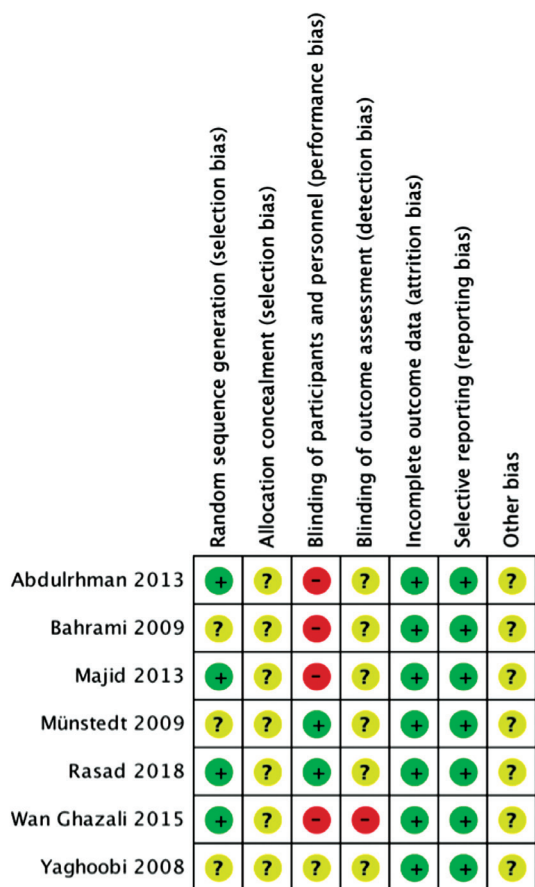
Figure 3 - Risk of bias summary showing the review authors' judgements about each risk-of-bias item for each included study.

the less, small trials are mostly not methodologically airtight, are mostly conducted in selected populations, and have been reporting advantageous effects more than larger trials. The results of the review are therefore inconclusive.

Experimental evidence has indicated that the consumption of natural honey may have a beneficial effect on the lipid profile.[9,17] particular, the literature suggests that the ingestion of natural honey and the reduction in CVD risk are linked,[5,6] as the flavonoids will prevent the oxidation of low-density lipoprotein, as shown in-vitro, which may take a part in coronary heart disease (CHD) prevention.[18] Additionally, these antioxidant functions' is to inhibit acyl-CoA cholesterol acyltransferase 2 (ACAT2), up-regulating LDL receptor and activating CYP7A1. Once the receptor is activated (up-regulated), the LDL clearance from the circulation will be more.

One of the suggested mechanisms of how honey changes the lipid profile is by the niacin-like substances' properties.[19] Sustained niacin release is proven to be the most effective modifier of lipids.[20,21] Aliphatic compounds, benzene derivatives, norisoprenoids, and maillard reaction products are examples of niacin-like substances found in honey. Another suggested mechanism is that honey acts on the parasympathetic system to abundantly release insulin.[22]

Furthermore, Niacin decreases the mobilization of fatty acid from adipose tissue when taken adequately. This produces rapid and large reduction in the levels of triglycerides. Thus, the liver going to secret smaller

Study or Subgroup	Experimental			Control			Weight	Mean Difference IV, Fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Abdulrhman 2013	-19.8	12.5	10	-7.2	13.2	10	17.0%	-12.60 [-23.87, -1.33]
Bahrami 2009	-36.9	29.35	25	-19.7	23.3	23	9.7%	-17.20 [-32.13, -2.27]
Majid 2013	-15.47	19.8	32	11.22	16.8	31	26.3%	-26.69 [-35.75, -17.63]
Münstedt 2009	-0.3	31.9	30	4.7	24.47	30	10.4%	-5.00 [-19.39, 9.39]
Rasad 2018	-6.3	21.4	30	1.07	22.61	30	17.4%	-7.37 [-18.51, 3.77]
Wan Ghazali 2015	-10.04	30.39	32	3.48	24.3	32	11.9%	-13.52 [-27.00, -0.04]
Yaghoobi 2008	-7	34.48	38	3	27.7	17	7.3%	-10.00 [-27.13, 7.13]
Total (95% CI)			**197**			**173**	**100.0%**	**-14.97 [-19.61, -10.32]**

Heterogeneity: Chi^2 = 10.69, df = 6 (P = 0.10); I^2 = 44%
Test for overall effect: Z = 6.32 (P < 0.00001)

Figure 4 - Forest plot of comparison showing the experimental (honey) versus control groups (outcome 1: total cholesterol).

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Abdulrhman 2013	9.1	5.68	10	-0.9	7.55	10	3.5%	10.00 [4.14, 15.86]
Bahrami 2009	6.9	9.2	25	1.1	8.53	23	4.8%	5.80 [0.78, 10.82]
Majid 2013	1.71	4.1	32	0.62	2.7	31	41.4%	1.09 [-0.62, 2.80]
Münstedt 2009	-2.8	12.2	30	-2.3	8.3	30	4.3%	-0.50 [-5.78, 4.78]
Rasad 2018	2.94	4.67	30	-3.65	5.32	30	18.9%	6.59 [4.06, 9.12]
Wan Ghazali 2015	-1.93	5.28	32	0.38	4.1	32	22.5%	-2.31 [-4.63, 0.01]
Yaghoobi 2008	2	9.16	38	2	9	17	4.5%	0.00 [-5.18, 5.18]
Total (95% CI)			197			173	100.0%	1.78 [0.68, 2.88]

Heterogeneity: Chi^2 = 37.66, df = 6 (P < 0.00001); I^2 = 84%
Test for overall effect: Z = 3.18 (P = 0.001)

Favours [control] Favours [experimental]

Figure 5 - Forest plot of comparison showing the experimental (honey) versus control groups (outcome 2: HDL cholesterol).

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Abdulrhman 2013	-25	14.1	10	27.2	12.19	10	10.8%	-52.20 [-63.75, -40.65]
Bahrami 2009	-17.7	16.93	25	-11	14.75	23	17.9%	-6.70 [-15.67, 2.27]
Majid 2013	-11.21	13.1	32	8.87	14.3	31	31.4%	-20.08 [-26.86, -13.30]
Münstedt 2009	4	23.3	30	7.8	18.8	30	12.6%	-3.80 [-14.51, 6.91]
Rasad 2018	-13.8	18.1	30	8.47	14.2	30	21.3%	-22.27 [-30.50, -14.04]
Wan Ghazali 2015	-9.3	94.3	32	0	19.37	32	1.3%	-9.30 [-42.65, 24.05]
Yaghoobi 2008	-8	32	38	3	29.41	17	4.8%	-11.00 [-28.29, 6.29]
Total (95% CI)			197			173	100.0%	-18.99 [-22.79, -15.20]

Heterogeneity: Chi^2 = 48.54, df = 6 (P < 0.00001); I^2 = 88%
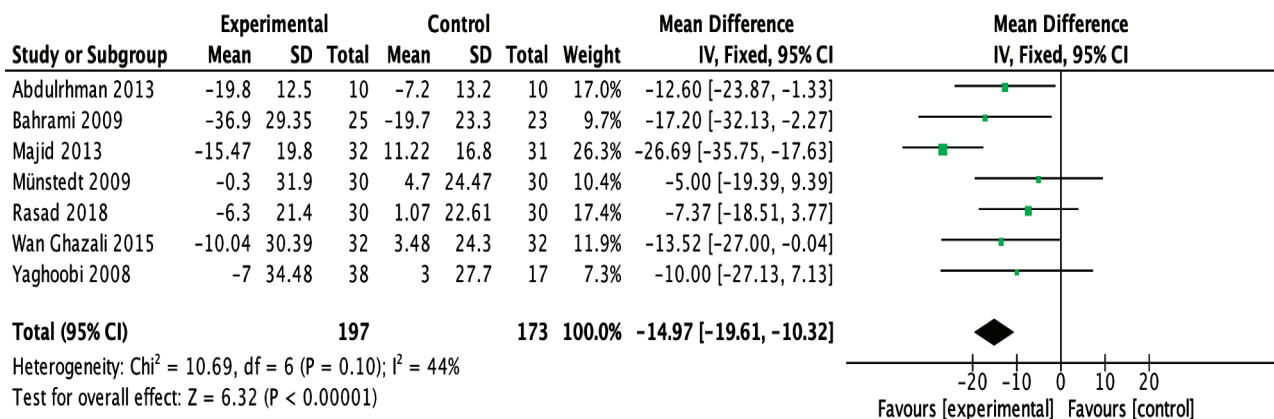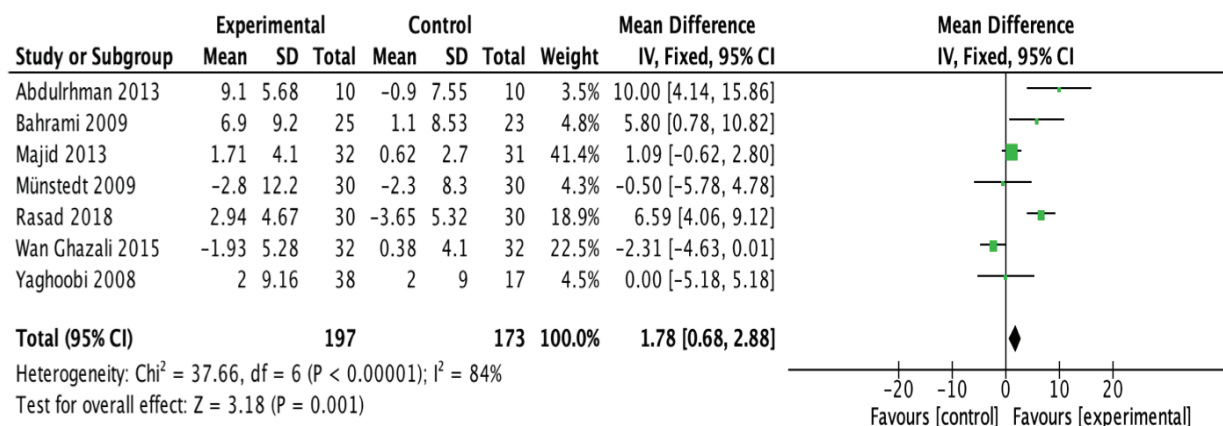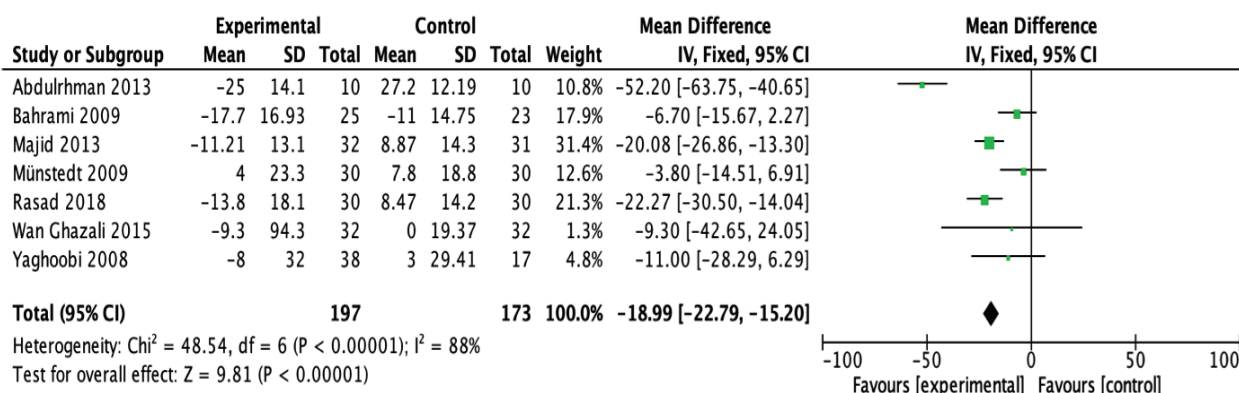Test for overall effect: Z = 9.81 (P < 0.00001)

Favours [experimental] Favours [control]

Figure 6 - Forest plot of comparison showing the experimental (honey) versus control groups (outcome 3: LDL cholesterol).

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Abdulrhman 2013	-17.8	12.48	10	8.8	12.81	10	28.2%	-26.60 [-37.68, -15.52]
Bahrami 2009	-42	48.6	25	-25.6	45.25	23	4.9%	-16.40 [-42.95, 10.15]
Majid 2013	-5.31	25.05	32	12.4	12.47	31	36.6%	-17.71 [-27.44, -7.98]
Münstedt 2009	14	57.12	30	20.4	65.16	30	3.6%	-6.40 [-37.41, 24.61]
Rasad 2018	17.23	25.97	30	-21.3	33.34	30	15.1%	38.53 [23.41, 53.65]
Wan Ghazali 2015	11.51	39.87	32	13.28	38.01	32	9.5%	-1.77 [-20.86, 17.32]
Yaghoobi 2008	-17	48.09	38	-1	79.24	17	2.1%	-16.00 [-56.65, 24.65]
Total (95% CI)			197			173	100.0%	-9.68 [-15.56, -3.80]

Heterogeneity: Chi^2 = 51.65, df = 6 (P < 0.00001); I^2 = 88%
Test for overall effect: Z = 3.23 (P = 0.001)

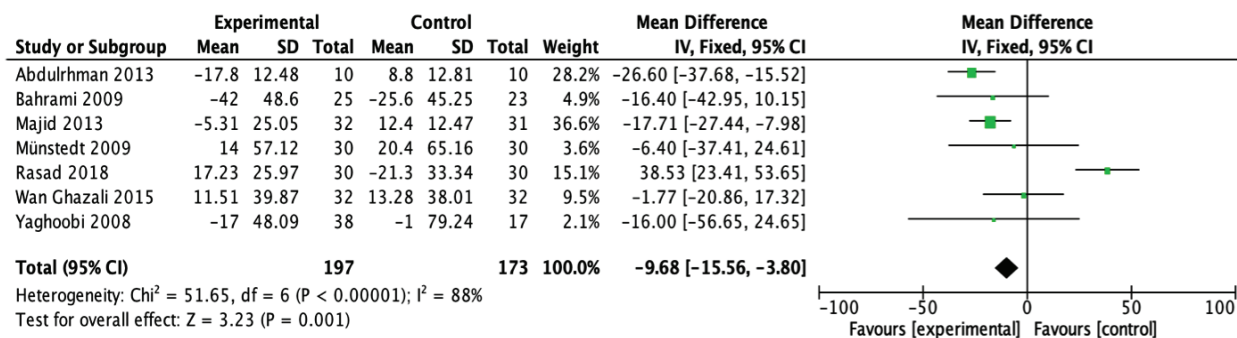Favours [experimental] Favours [control]

Figure 7 - Forest plot of comparison showing the experimental (honey) versus control groups (outcome 4: triglycerides).

amount of VLDL with smaller amount of triglycerides. Apolipoprotein B gathers VLDL cholesterol, yet the effect of niacin activity may inhibit its secretion, resulting in less VLDL cholesterol. Triglycerides levels can be reduced as well by the enhancement of VLDL catabolism.[20]

Our comprehensive search across major databases for interventions involving natural honey. When necessary, authors were contacted, and the list of references was screened and reviewed. The well-known systematic review steps starting from screening, inclusion, and exclusion through data extraction were executed by 2 independent reviewers. Entry and analysis of the date were carried out by one reviewer and reviewed by the second one to assure accuracy of the data entered. We decided to limit our review to interventions solely investigating natural honey avoided potential confounding effects. In addition, because of the small number of trials in this review, the methodological quality reporting was considered limited, and in more than half of the included trials, the assessment of risk of bias was unclear.

In conclusion, natural honey in our review expressed a statistically significant reduction in triglycerides, LDL, and total cholesterol. Honey increased HDL significantly. Noteworthy, honey can be recommended for patients with dyslipidemia if consumed in small quantities not more than 75g as used by most of the included studies whether alone or dissolved in water. The impact on clinical outcomes such as cardiovascular mortality and morbidity needs to be evaluated in large studies.

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